16. Trosko JE, Chang CC. Nongenotoxic mechanisms in carcinogenesis: role of inhibited intercellular communication. In: Banbury Report 31: Carcinogen Risk Assessment: New Directions in the Quantitative and Qualitative Assessment Aspects (Hart RW, Hoerger FD, eds). Cold Spring Harbor, NY:Cold Spring Harbor Laboratory, 1988;139–174.
17. Sai K, Upham BL, Kang K-S, Hasegawa R, Inoue T, Trosko JE. Inhibitory effect of pentachlorophenol on gap junctional intercellular communication in rat liver epithelial cells in vitro. Cancer Lett 130:9–17 (1998).
18. Warren ST, Dolittle DJ, Chang CC, Goodman JI, Trosko JE. Evaluation of the carcinogenic potential of 2,4-dinitrofluorobenzene and its implications regarding mutagenicity testing. Carcinogenesis 3:139–145 (1982).
19. Upham BL, Weis LM, Trosko JE. Modulated gap junctional intercellular communication as a biomarker of PAH epigenetic toxicity: structure–function relationship. Environ Health Perspect 106(suppl 4):975–981 (1998).
20. Rummel AM, Trosko JE, Wilson MR, Upham BL. Polcyclic aromatic hydrocarbons with bay-like regions inhibited gap junctional intercellular communication and stimulated MAPK activity. Toxicol Sci 49:232–240 (1999).
21. Rosenkranz M, Rosenkranz HS, Klopman G. Intercellular communication, tumor promotion and non-genotoxic carcinogenesis: relationships based upon structural considerations. Mutat Res 381:171–188 (1997).
22. Temme A, Buchmann A, Gabriel HD, Nelles E, Schwarz M, Willecke K. High incidence of spontaneous and chemically induced liver tumors in mice deficient for connexin32. Curr Biol 7:713–716 (1997).

Tumor Promoters: Tennant's Response

Trosko indeed presents an alternative and valid position on the nature of tumor promotion. It is certainly true that disrupted intracellular communication is an important component in the promotion and development of tumors and may be another pathway by which repetitive exposure to nongenotoxic carcinogens and genotoxic carcinogens results in altered heritable cell phenotypes. The editorial in *EHP* (*1*) was not meant to be an exhaustive catalog of all of the various mechanisms by which nongenotoxic carcinogenesis can occur. It is clear that intercellular and intracellular signaling via endocrine, exocrine, paracrine, and autocrine pathways is critical in maintaining phenotypic stability. Evidence also suggests that when gap junctional intracellular communication pathways are disrupted, the frequent consequence is altered gene expression. Preliminary experiments (*2*) do not suggest that exposure of skin to nongenotoxic carcinogens or to a tumor promoter results in a bewildering pattern of changes in gene expression. We believe that it is plausible that analysis of time-dependent changes in the pattern of gene expression will provide an understanding of cell-signaling pathways that are altered by chemical exposure. It may also result in the recognition of biomarkers of critical events in the neoplastic process that will include disrupted gap junctional communication.

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References and Notes

1. Tennant R. What is a tumor promoter? [Editorial]. Environ Health Perspect 107:A390–A391 (1999).
2. Tennant R, et al. Unpublished data.

Correction and Clarification

In the November EHPnet article "Connecting for Kids" [*EHP* 107:A553], we wrote of the Children's Environmental Health Network (CEHN): "Currently, this public interest organization is lobbying the U.S. Environmental Protection Agency (EPA) to require testing of pesticides for their effects on the developing nervous systems of children." Although the CEHN is an advocacy group, it does not lobby specific pieces of legislation. *EHP* regrets any confusion this wording may have caused.